PATENT SPECIFICATION

NO DRAWINGS

822,695

Date of Application and filing Complete Specification: March 18, 1958.
No. 8718/58.
Application made in Germany on April 11, 1957.
Complete Specification Published: Oct. 28, 1959.

Index at acceptance:—Class 2(3), C2(A2: A5: A9: A14: S16).
International Classifcation:—C07c.

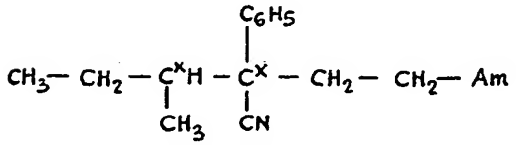
COMPLETE SPECIFICATION

Therapeutically Effective Amino-Nitriles and method of preparing the same

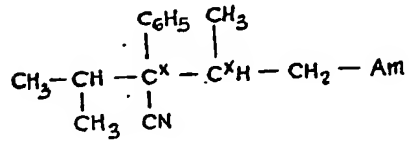
We, KALI CHEMIE AKTIENGESELLSCHAFT, of Hans-Böckler-Allee 20, Hannover, Germany, a body corporate organised under the laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to therapeutically effective amino-nitriles and to a method of preparing the same.

Amino-nitriles containing two asymmetrical carbon atoms are already known; thus for instance, according to Specification No. 765,510, amino-nitriles, which are effective analgesics, can be obtained of the general formula I and II



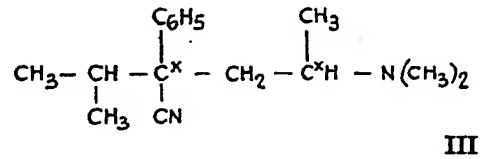
I



II

in which Am denotes a dialkyl-amino group or a cyclic amino group.

However, an amino-nitrile of the following composition III has not hitherto been known:—



III

In this amino-nitrile the two asymmetrical carbon atoms denoted by *x* are not adjacent but are separated by a carbon atom and the substance has a pronounced cough inhibiting effect.

The anti-tussal effect of compound III was tested in guinea pigs under urethane narcosis. The cough stimulus was produced by electrically tickling the trachea with a blunt platinum electrode. The megatest was used as an irritation generator. Rectangular impulses of a duration of 5 millisecs each, an intensity of 5 to 15 milliamps, and a frequency of 10 c/sec were generated. The cough contractions of the abdomen were mechanically recorded. Evaluation was qualitative, all those animals being regarded as "positive" which were completely unresponsive to electric tickling. The mean effective dosage (ED 50) was determined by plotting a dosage effect curve according to Litchfield and Wilcoxon.

The mean effective dosage of compound III was 5.4 mg/kg i.v. The ED 50 is therefore better than that of codeine phosphate (7 mg/kg i.v.).

This result could not have been expected and is particularly surprising because the amino-nitriles obtained according to Specification No. 765,510 exhibit no cough inhibiting effect.

The result of the pharmacological tests performed with compound III supra were borne out by clinical tests.

The preparation of the novel cough suppressing substance III is characterised in that α-isopropyl-phenylacetonitrile is reacted in the presence of sodium amide with 2-dimethylamino-1-chloropropane to form α-(isopropyl)-α - (β - dimethylaminopropyl) - phenylacetonitrile (III) and that, if desired, acid addition salts of the reaction product are prepared.

Alternatively, compound III according to the invention may be prepared by reacting α-(β - dimethylaminopropyl) - phenylacetonitrile in the presence of sodium amide with an isopropyl halide.

The invention will be illustrated by the following Examples:—

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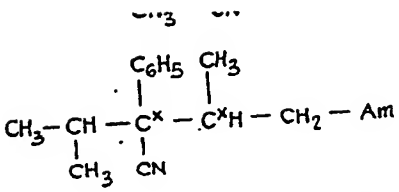
ERRATA

SPECIFICATION No. 822,695

Page 1, line 1, after "Kali" insert "-"
Page 2, line 29, *after* "dimethylaminopropyl)" *insert* "-"

THE PATENT OFFICE
10th June, 1960



I

II

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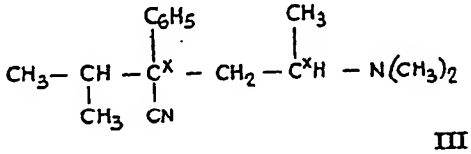

III

In this amino-nitrile the two asymmetrical carbon atoms denoted by *x* are not adjacent

[illegible] (Kg L.V.).

This result could not have been expected and is particularly surprising because the amino-nitriles obtained according to Specification No. 765,510 exhibit no cough inhibiting effect.

The result of the pharmacological tests performed with compound III supra were borne out by clinical tests.

The preparation of the novel cough suppressing substance III is characterised in that α-isopropyl-phenylacetonitrile is reacted in the presence of sodium amide with 2-dimethylamino-1-chloropropane to form α-(isopropyl)-α-(β-dimethylaminopropyl)-phenylacetonitrile (III) and that, if desired, acid addition salts of the reaction product are prepared.

Alternatively, compound III according to the invention may be prepared by reacting α-(β-dimethylaminopropyl)-phenylacetonitrile in the presence of sodium amide with an isopropyl halide.

The invention will be illustrated by the following Examples:—

EXAMPLE 1:—

α - (isopropyl) - α - (β - dimethylaminopropyl)-phenylacetonitrile (III):—

140 c.c. of benzene and 24 g of α-(isopropyl)-phenylacetonitrile were added to 7.5 g of sodium amide. Whilst being stirred the mixture was heated to boiling point for one hour under reflux. After cooling, 25 g of 2-dimethylamino-1-chloropropane, dissolved in benzene, were added and the mixture was again heated to boiling point for four hours whilst being stirred. After completion of the reaction, water was added to the contents of the flask and the benzenic solution separated off. After shaking this out with hydrochloric acid the acid solution was adjusted to alkalinity. The separated oil was taken up in ether and the ethereal solution dried with sodium sulphate. After the ether had been distilled off the amino-nitrile thus obtained was distilled in vacuo. It had a $b.p._3 = 138—146°C.$ and produced a citrate of m.p. = 63—64°C. (in alcohol/ether) which was readily soluble in water.

EXAMPLE 2:—

α - (isopropyl) - α - (β - dimethylaminopropyl)-phenylacetonitrile (III):—

120 c.c. of benzene and 16.3 g of α-(β-dimethylaminopropyl)phenylacetonitrile were added to 4 g sodium amide. Whilst being stirred the mixture was heated to boiling point for one hour. 11 g of isopropyl bromide, dissolved in a little benzene, were then added and the mixture again heated to boiling point for four hours whilst being stirred. Further processing was as described in Example 1. The amino nitrile obtained was identical with the compound prepared according to Example 1 and formed a tartrate of m.p. = 64°C. (in ether) which was readily soluble in water.

The 16.3 g of α-(β-dimethylaminopropyl)-phenylacetonitrile used above were prepared by reacting 15 g of benzyl cyanide with 17.5 g of 2-dimethylamino-1-chloropropane in the presence of sodium amide (6.5 g). The nitrile boiled at $b.p._6 = 134—139°C.$

WHAT WE CLAIM IS:—

1). α - (Isopropyl) - α - (β - dimethylaminopropyl)-phenylacetonitrile.

2). Acid addition salts of α-(isopropyl)-α-(β - dimethylaminopropyl) - phenylacetonitrile.

3). Citrate of α-(isopropyl)-α-(β-dimethylaminopropyl)-phenylacetonitrile.

4). A method of preparing α-(isopropyl)-α-(β-dimethylaminopropyl) - phenylacetonitrile, characterised in that α-isopropyl-phenylacetonitrile is reacted with 2-dimethylamino-1-chloropropane in the presence of sodium amide.

5). A method of preparing α-(isopropyl)-α-(β-dimethylaminopropyl) - phenylacetonitrile, characterised in that α-(β-dimethylaminopropyl)-phenylacetonitrile is reacted with an isopropyl halide in the presence of sodium amide.

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